UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,306	03/23/2001	Wen Y. Chen	035879/0120	4654

7590 05/14/2002

Charles F. Schill
FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, DC 20007-5109

EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 05/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/815,306	Applicant(s) CHEN ET AL.	
	Examiner Christopher H Yaen	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *11-21,23,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,22,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in Paper No. 9 is acknowledged. Claims 1-10, 22, and 24-25 are examined on the merits.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-10, 22, and 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. In regards to claim 1 and dependent claims thereof, in the recitation of the phrases/term: *"receptor antagonizing domain"*, it is indefinite and vague because the phrase can be applied to virtually any protein that antagonizes a receptor; *"positive immunomodulator domain"*, it is indefinite and vague because a positive immunomodulatory response can at times mean a decrease in immune cell response, and *"effective"*, it is not clear how treatment of cancer using the protein containing a receptor-antagonizing domain and an immunomodulator domain, is to effect the end result. Clarification is required.

5. In regards to claims 9 and 10 in the recitation of the phrase *"conservative variant"*, it is indefinite and unclear as to what this variation or modification would be, that would 1) constitute a conserved modifcation, and 2) what it is exactly. Clarification is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-10, 22, and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer cells that over express prolactin receptors, a method of treating cancer using a protein containing a prolactin receptor antagonizing domain and an immunomodulator region of IL2, and a method of treat cancer using a protein having an amino acid sequence of SEQ ID No. 1, does not reasonably provide enablement for a method of treating any cancer, a method of treating cancer using a protein containing IL-12 or IFNγ, and a method of treating cancer using a protein that is a truncated form or conservative variants of SEQ ID No. 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-10, 22, and 24-25 are drawn to a method of treating cancer, comprising the administration of a proteins that contains a receptor-antagonizing domain and an immunomodulator domain, wherein the receptor antagonizing domain is a prolactin-antagonist domain, also an apoptosis-promoting domain, characterized by a single amino acid substitution (SEQ ID No.1), and the immunomodulator domain is an IL-2, IL-12, or IFNγ. The instant specification while being enabling for the above mentioned limitations, is virtually silent with regard to any other limitations, set forth *supra.* Because the instant application is silent in this regard, one of ordinary skill would be

forced into undue experimentation in order to practice the claimed invention using all of the limitations set forth in the instant application. The instant application invites the skilled artisan to experiment.

The factors which must be considered in determining undue experimentation are set forth in *In re Wands* 8 USPQ2d 1400. The factors include: (1) quantity of experimentation, (2) the amount of guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the predictability of the art and, (7) breadth of the claims.

With regards to factors one and two cited above, the quantity of experimentation needed to determine what other types of cancer could be treated with this protein, the effects caused by switching IL-2 with IL-12 and IFNγ, and utilizing a truncated or conservative variant of the SEQ ID No. 1, is high because cancers all have different etiologies and characteristics which require different methods and forms of treatment (Macieira-Coelho A Biogerontology 2001;2(3):179-92), the elicitation of immune response caused by IL-2 and that caused by IL-12 and IFNγ are known to be different (Mocellin S *et al.* J. Immunother 2001 Sep-Oct; 25(5):392-407), and the truncated form of the protein or conservative variants to be used are not distinctly identified, causing the skilled artisan to look for an area to be truncated or a variant of the antagonist. The instant specification is silent in this regard and the disclosure that has been provided is seen as not adequately providing guidance in the written description for accomplishing such.

With regards to factors four, five and six cited above, it is noted that there is a great deal of unpredictability associated with treating cancer. The instant specification fails to provide specific methodological steps, outcomes or any indication that: cancers other than those over expressing prolactin receptors can be treated; if switching of IL-2 with IL-12 or IFNγ will or will not effect the outcome of treatment; or whether or not a truncated form or conservative variant would work in the instantly claimed invention. The art at the time the invention was made fails to establish with any definite certainty that antagonizing a receptor, especially a prolactin receptor, could be an effective form of treatment of cancer in general, or that IL12 or IFNγ localized to a tissue could elicit the same effect as a localized IL-2 cytokine.

With regards to factors three and seven cited above, it is noted that the working examples are limited to treatment methods for cancers over expressing prolactin receptors, utilizing a prolactin antagonist fused to IL-2. Such is not seen as sufficient to support the breadth of the claims, wherein the scope of the claims encompasses treatment of any cancer, using cytokines other than IL-2, and an antagonizing domain other than prolactin of SEQ ID No. 1. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art ho to use applicant's alleged discovery, not how to find out how to use it for themselves., see *In re Gardner et al.* 166 USPQ 138 (CCPA 1970).

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, and 3-4, and are rejected under 35 U.S.C. 102(b) as being anticipated by Lode *et al.* (Proc Natl Acad Sci USA 1999 Feb; 96(4):1591-1596). Claims 1, and 3-4 are drawn to a method of treating cancer, comprising administrating a protein having a receptor antagonizing domain and a positive immunomodulator domain. Lode *et al.* disclose of a method of treating tumors and metastatic lesions by using a protein containing an antagonizing domain and an immunomodulator region (see abstract, introduction section (pg 1592 column 1), result section (pg 1592 column 1).

10. Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Gillies *et al.* (J. Immuno 1998; 160(12):6195-203. Claim 5 is drawn to a method of treating cancer comprising administering to a patient an amount of a protein having a receptor-antagonizing domain and a positive immunomodulator domain, wherein the positive immunomodulator domain is an IL-12. Gillies *et al.* disclose of an antibody that binds to a receptor, and hence a receptor- antagonist that is fused to a cytokine, namely IL-12. Furthermore, Gillies *et al.* disclose of using this fusion protein as a method treating cancer. Therefore, the invention as claimed is anticipated.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lode *et al.* in view of Bulfone-Paus S *et al.* (Transplantation 2000 Spr 15;69(7):1386-91). Claim 24 is drawn to a method of treating cancer comprising the administration of a protein containing a receptor antagonizing domain and an immunomodulator domain, wherein the receptor antagonizing domain is a apoptosis promoting domain.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Lode *et al.* fail to describe a receptor antagonizing domain that is a apoptosis promoting domain. Bulfone-Paus S *et al.*, however, do disclose of a fusion protein wherein the receptor antagonizing domain is an apoptosis promoting domain fused to a immunomodulator molecule, IL-2.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to devise of a method of using a protein containing a receptor antagonizing domain which is an apoptosis promoting domain, fused to an immunomodulator region, because the prior art provides sufficient motivation to practice the invention as claimed. The suggestion for doing what applicant has claimed is that because it was known in the art that a protein containing a receptor antagonizing

domain and an immunomodulator region was already known in the art to be used as a cancer treating protein. Therefore it would have been *prima facie* obvious at the time of the invention to substitute or replace the receptor antagonizing domain with a receptor antagonizing domain, wherein the receptor antagonizing domain is an apoptosis promoting domain, because it was known to those skilled in the art at the time of the invention that a fusion protein containing the essential elements of the instant invention was being used to treat patients with cancer. It is also a commonly excepted belief that apoptosis of cancer cells is a desirable effect and that any protein that is able to promote such an event to eradicate cancer cells would be a valuable product and method. Therefore, it would have been obvious to substitute the receptor antagonizing domain of the prior art with a receptor antagonizing domain which also promoted apoptosis.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art unit 1642
May 2, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600